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(57) Abstract

The invention relates to a new use of growth hormone, wherein growth hormone, for instance recombinant growth hormone, preferably human recombinant growth hormone, is used to manufacture a pharmaceutical preparation to treat patients with a low triiodothyronine level. A low triiodothyronine level can be the result of the low T3 syndrome as described in the literature. The low T3 syndrome in a patient can be caused by a large number of clinical conditions, which can be both physical and mental. The use of medicines can also cause the low T3 syndrome. According to the invention one or more thyroid hormones and/or anabolic steroids can be administered simultaneously with growth hormone.

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NEW USE OF GROWTH HORMONE

The present invention relates to a new use of growth hormone.

A large number of clinical conditions is found to be characterized by a low level of triiodothyronine (T3) in serum. In the literature this phenomenon is called "low T3 syndrome" or "euthyroid sick syndrome" (see also for a survey Docter et al., Clinical Endocrinology (1993) 39, 499-518 and Wartofsky and Burman, Endocrine Reviews (1982) 3(2), 164-217). The low T3 syndrome occurs in both physical and mental disorders in addition to disorders caused by the use of medicines. It is thus known from the literature that a low T3 syndrome is found in inter alia systemic non-thyroidal diseases, in liver disorders, after stress or an operation, in chronic kidney failure, in an older sick person, after the use of particular medicines etc.

It has been found that the critically ill patient can be mentioned as another example of a patient with a low T3 syndrome. This can be defined as a person who has undergone a major surgical operation or serious traumatic injury or is recovering therefrom, or is suffering from a serious illness and whose vital functions have to be supported by means of mechanical and/or pharmacological means, such as mechanical ventilation, extra corporeal cardiac support, renal replacement therapy, inotropic support etc..

Prolonged critical illness can be considered a state of chronic severe stress. This stress can be generated by different factors such as sepsis, hypoxy of the tissues, multiple organ failure, infections, wound of healing, pain, fear, immobilization or even by the supporting measures and therapeutic medicines themselves. This state of chronic stress appears to result in a complex of pathophysiological processes which ultimately result in a clinical picture characterized by a catabolic condition, a disturbed immune function and the generation of catecholamines and cytokines. In the long term the catabolic condition limits in

particular the capacity of the patient to take care of himself and this slows down recovery.

Critically ill patients are often to be found in the intensive care unit of a hospital. In intensive care medicine an infusion with a low dose of dopamine (2-5 μg/kg/min) is often administered to support the patient. It is thought that dopamine provides inotropic support and optimization of the perfusion of the intestines and the kidneys. Few clinical studies are however available which suggest that dopamine actually serves this latter purpose. The different effects of dopamine can be attributed to its inotropic or direct tubular or diuretic action. Whether dopamine is really favourable for the kidney function still remains unanswered up to the present time. In large doses dopamine could theoretically be valuable as a vascular dilation agent for the intestines. However, definitive clinical data is also unavailable here.

Other inotropic agents are currently available in intensive care medicine. Dopamine nevertheless remains the first choice supportive agents for many doctors because of its superior inotropic properties and the possible optimization of the intestinal and kidney perfusion. Dopamine is therefore used extensively in cases of critically ill, septic, post-operative or post-traumatic infants, toddlers, small children and older children as well as adults, this sometimes for days, weeks or even months.

During the research which resulted in the present invention it was established that treatment with dopamine induces additional changes which can worsen the condition of the critically ill patient. It has been discovered that dopamine causes inter alia a decrease in the level of triiodothyronine (T3) (see for further details the doctoral thesis by Dr. G. van den Berghe "Dopamine and pituitary hormones in critical illness" which was publicly defended on 19 April 1994 and the content of which is interpolated herein by reference. The thesis also forms part of the priority document of the present invention.) As already cited above, it is further known from the literature that

medication with other medicines and a large number of clinical symptoms can likewise be characterized by a low T3 level.

The experiments described in the thesis demonstrate that interruption of the dopamine infusion in adult polytrauma patients who had already undergone prolonged treatment with dopamine resulted in an immediate rise in the T3.

It was also found that in the case of the said patients growth hormone was secreted only in pulses, wherein a low secretion amplitude was observed. This pattern indicates growth hormone deficiency which appears to be intensified by dopamine. This observation in non-septic polytrauma patients is in contrast to earlier observations in the case of septic, post-operative patients, for whom an increased basal growth hormone concentration in serum was reported.

It has further been found from the research that due to the dopamine infusion the Euthyroid Sick Syndrome (ESS) is induced or intensified in critically ill patients through suppression of TSH secretion, lowering of T4 and T3 concentrations and the T3/rT3 ratio.

In experiments with newborn babies and children recovering from cardiovascular surgical operations it was found that dopamine infusion resulted in a reversible suppression of different hypophysic functions. In the case of newborn babies and infants it was found that the growth hormone concentrations rose immediately after the dopamine treatment was stopped. The T3 level in serum also increased.

These findings suggest that a low T3 level can be linked to growth hormone deficiency. According to the invention is established for the first time that through administering of growth hormone the symptoms of the low T3 syndrome can be reduced or even eradicated. The patient will quickly feel better and in the case of critically ill patients they can even be removed sooner from the support equipment such as respirator and the like.

The invention therefore relates to the use of growth hormone to manufacture a pharmaceutical preparation for

treating patients with a low triiodothyronine level which is for instance the consequence of the low T3 syndrome. This low T3 level can already be documented but the use may also be applicable to patients in whom a low T3 level is anticipated on the basis of the observed symptoms, without this being already determined. Treatment can already be started when a low T3 level is expected. The treatment with growth hormone is of course not limited to the above described critically ill patient but is applicable to any mentally or physically ill patient whose disorder comprises a low T3 syndrome. Understood by "low T3 level" is a level of total T3 in serum lying below the level of about 80 ng/dl qualified as normal. Understood by "low T3 syndrome" is having a low T3 level in combination with a low or normal TSH (thyroid stimulating hormone) level. It is found in practice that the T3 level in sufferers of low T3 syndrome may even lie below 25 ng/dl.

According to the invention both natural and recombinant growth hormone can in principle be used. In practice however, recombinant growth hormone will usually be used.

In addition, peptides or other molecules which stimulate secretion of growth hormone can be applied, on their own or in combination with growth hormone. It will be apparent to the skilled person which peptides or other molecules are suitable for this purpose. It is important herein that the growth hormone secretion of the body is stimulated.

Pharmaceutical compositions which contain growth hormone as the active ingredient or which stimulate the endogenous production of growth hormone and which can be used for treating patients with a low T3 level in the serum will be administered by enteral means, intravenously, subcutaneously or intramuscularly. The pharmaceutical compositions according to the invention can take the form of oral forms of medication such as solutions, suspensions, emulsions, powders, capsules or tablets, or injectable forms of medication. The compositions can be prepared by combining (e.g. mixing, dissolving etc.) the active compound with pharmaceutically acceptable diluents of a neutral character

(such as aqueous or non-aqueous solvents, stabilizers, emulsifiers, detergents, additives etc.), and further with colouring agents if necessary. The concentration of the active ingredient in a therapeutic composition can vary between 0.1 and 100% depending on the specific situation and the method of administration. The dose of the active ingredient that is administered can further vary between 0.05 IU and 1.0 IU per kg body weight (this corresponds roughly with 0.03-0.56 ng/kg).

Clinical tests with patients who had undergone a lung transplant or a heart-lung transplant and who as a result were being nursed in the intensive care unit have shown that the administering of growth hormone was accompanied by the recovery of the patients.

Further situations with a low T3 level in serum, wherein the use of growth hormone could provide relief and/or cure are premature birth, fasting, undernourishment, anorexia nervosa, depression, anxiety syndromes, liver or kidney disfunction, systemic illness, chronic heart decompensation, COLD, sepsis, trauma, post-operative conditions, critical illness, the use of medicines such as propylthiouracyl, glucocorticoids, amiodaron, d-propanolol, oral cholecystographic agents, somatostatine, dopaminergic medication or an increased endogenous dopamine level etc. Old age is also possibly associated with the low T3 syndrome. It has been found in addition that disorders occurring under the influence of stress are likewise linked to a low T3 level. Growth hormone according to the invention can also be used with psychiatric patients.

Dopaminergic medicines which directly or indirectly cause a low T3 level are dopamine, dopamine-agonists such as bromocryptine, cabergoline, epinine etc., dopamine precursors and precursors of dopamine-agonists such as ibopamine. Understood by "dopamine-agonists" are compounds which have an activity corresponding with dopamine. Understood by "dopamine-precursors" are compounds which are converted in the body or otherwise into dopamine. Understood by "precursors of dopamine-agonists" are substances which

are converted in the body or otherwise into a dopamine-agonist.

The invention further relates to pharmaceutical compositions which contain one or more thyroid hormones in addition to the growth hormone and a pharmacologically acceptable diluent. In addition can be applied a combination of growth hormone with anabolic steroids, optionally supplemented with thyroid hormones. Understood by "thyroid hormones" are triiodothyronine (T3) and thyroxine (T4). Addition of thyroid hormones can immediately obviate a deficiency in this area. Anabolic steroids provide a reversal of the catabolic condition. The action of the growth hormone is additionally supported in such "cock-tails". Examples of such anabolic steroids are androgens, oestrogens and their natural or synthetic analogues.

The present invention will be further elucidated with reference to the accompanying examples which are only given by way of illustration and which do not have the intention of limiting the invention in any way. Patients are described in the examples whose low T3 syndrome was caused partially by dopamine medication. This is however only a model. In analogy therewith growth hormone, optionally in combination with thyroid hormones and/or anabolic steroids, can be used for treating low T3 syndrome which may be caused in any other way whatever.

EXAMPLES

EXAMPLE 1

1. Introduction

Recombinant growth hormone (also referred to hereinafter as "GH") has been available since 1985 for therapeutic applications which are not strictly associated with growth hormone deficiency. Because growth hormone has anabolic properties it is currently being evaluated as therapy in a diversity of catabolic conditions. It has now been found that extensive surgical interventions are associated with a catabolic condition which, despite optimal parenteral or internal feeding, is accompanied by a negative nitrogen

balance. A specific target group for GH treatment in catabolic condition is formed by patients who receive pharmacological doses of glucocorticoids, characterized by a loss of body protein, poor recovery of the tissues and an increased susceptibility to infections.

Heart, heart-lung and lung transplants are now being performed to an increasing extent on patients with a terminal disease of these organs. The nutritional condition prior to the operation is often poor, the stress after the operation is normally extreme and high doses of glucocorticoids are administered as part of the immune suppression. As a result hereof such patients run a high risk of developing a serious catabolic condition which could in turn have a further adverse effect on post-operative progress.

2. Experimental conditions

Three patients, 1 man of 19 years of age with cystic fibrosis and 2 women of respectively 17 and 27 with Eisenmenger syndrome, underwent respectively a double lung transplant and a heart-lung transplant. The man is further designated as patient 2, while the woman of 17 is called patient 1 and the woman of 27 patient 3. All three patients were cared for in the intensive care unit after the transplants. Their progress immediately after the operation was hindered by further surgery relating to haemorrhage, sepsis, lung hypertension, kidney insufficiency, catabolic condition and acute rejection reactions, which were treated with extra boluses with a high dose of glucocorticoids.

There further occurred additional problems of a high urea-nitrogen level in the blood, general weakness, dependence on ventilation and muscular weakness. Patient 1 further had a bilateral diaphragm paralysis after a surgical lesion caused by freezing of the phrenic nerves.

All these incidents prevented recovery in all three of the patients. Protracted and repeated efforts to remove these patients from the respirator failed despite maximum conservative treatment for a total duration of ventilation

of 62 days in the case of patient 1 and 14 days in the case of patients 2 and 3. This failure was attributed partly to the serious catabolic condition of these patients and a rescue treatment was therefore attempted with growth hormone (Genotropin, Pharmacia, Stockholm, Sweden).

The patients received a daily dose subcutaneously of 16 units (1 unit is 0.56 ng). The growth hormone concentrations in the serum prior to the therapy were lower than 5 μIU/ml (= 2.8 μg/l (ng/ml)). At the start of the treatment the urea-nitrogen levels in blood (BUN levels) were increased, while the serum concentrations of IGF-1, insulin and T3 were low.

Patient 1 received growth hormone for three weeks, while patients 2 and 3 were treated for two weeks. Within respectively 11, 7 and 5 days the condition of the patients was noticeably improved, they were successfully withdrawn from the respirators and the ventilation was finally terminated.

Recovery was linked to a decrease in BUN of more than 50%, while protein absorption was 1.5 g/kg/day.

In each patient the IGF-1 and insulin concentration in the serum increased at least fourfold. In two patients the rise in insulin concentration was partly of exogenous origin, since due to an increased glucose intolerance continuous infusion of human insulin had become necessary. The insulin dose was adjusted such that a blood glucose concentration of about 5.6 mmol/l was obtained. The glucose intolerance disappeared within 24 hours after the growth hormone therapy was interrupted.

After two weeks of therapy the T3 concentrations in serum were found to have risen by roughly 50%.

During the first week the creatinine removal, which is a measure for the glomerular filtration speed as a measure for the kidney function, rose in patient 1 from 18.2 to 32 ml/min and decreased in patients 2 and 3 from respectively 62 to 32 ml/min and from 108 to 70 ml/min. In all three patients the creatine removal thereafter remained stable.

Because fluid was retained the body weight increased quickly during the first few days to a maximum of respectively 20%, 16% and 11% above the weight before the treatment. The maximum fluid retained appeared at the beginning of the second week of the growth hormone medication. By administering diuretics (furosemide) retention of fluid decreased with continued growth hormone therapy.

During the growth hormone treatment no additional rejection or infection episodes occurred. At the end of the growth hormone therapy period the patients were discharged from the intensive care unit.

The results are further illustrated in the accompanying figure, in which BUN, serum IGF-1, insulin and T3 concentrations are shown for the patients 1, 2 and 3 at the start of the experiment (white bars) and after 1 week (hatched bars) and after 2 weeks (black bars) of GH therapy.

3. Discussion

The three patients presented here were in a clinical condition of catabolism considered hopeless and dependent on ventilation after a heart-lung or double lung transplant. The biochemical parameters confirm the clinical impression of the catabolic condition (high levels of BUN, low levels of IGF-1, insulin and T3) before the growth hormone therapy was started. All patients displayed an exceptionally rapid recovery, both clinically and biochemically, during the growth hormone therapy. The consistent fall in BUN together with the remarkable clinical improvement, the dramatic rise in circulating IGF-1, insulin and T3 concentrations together suggest a reversal of the catabolic condition.

The increased requirement of exogenous insulin in two patients confirms the earlier experience with the combined therapy of glucocorticoids and growth hormone (Horber et al., Diabetes (1991) 40, 141-149). It is remarkable that the insulin resistance induced by growth hormone was reversed within 24 hours after the therapy was interrupted. It could be concluded herefrom that a possible side-effect of the

growth hormone therapy rapidly disappears again after ending of this therapy.

It can be stated in conclusion that a treatment with a high dose of growth hormone can be favourable in reversing the catabolic condition and speeding up the process of critically ill patients becoming independent of ventilation after heart-lung or double lung transplant.

EXAMPLE 2

2.1 Diagnosis

Vasculitis, probably on autoimmune basis, was diagnosed in a male patient of 52 years of age. Accompanying symptoms were bulbous ulcer and arterial bleeding, secondary intestinal necrosis, fistulization and wound healing problems. The patient had undergone extensive and repeated surgical operations, such as progressive intestinal section resulting in "short bowel syndrome", combined with a high dose glucocorticoids treatment. In addition the patient displayed a low T3 syndrome, characterized by a TSH level of 0.01 mIU/l; a T4 level of 6.5 µg/dl; a T3 level of 49 ng/dl and a reverse T3 level of 155 ng/dl. Because no wound healing occurred and pronounced muscular atrophy and cachexia were observed, the patient was dependent upon ventilation.

2.2 Therapy

The patient was treated post-operatively with growth hormone and T4 for 42 days after the first extensive surgical treatment. The total duration of the treatment amounted to 54 days, whereafter the patient was discharged from the intensive care unit and was further cared for in abdominal medicine. On days 1 and 2 4IU of growth hormone were administered, on days 3-7 8 IU and on days 8-54 16 IU. On days 1 to 14 50 µg T4 was administered, thereafter 100 µg/day.

2.3 Evaluation

2.3.1. Clinical development

Within the first week of treatment the wound healing evolved from a completely atonal, open abdominal wound without any sign of scar tissue forming and even totally without fibrin formation, with persistent fistulization and bile leakage, to a very rapidly granulating wound with closure of fistulas and healing of the bile leak.

After 42 days of full ventilation the patient could, with growth hormone therapy, be withdrawn from mechanical respiratory support progressively and completely over a period of 14 days. This is a spectacular clinical improvement. On day 34, during the growth hormone therapy, the patient received another surgical revision, whereafter he could be withdrawn immediately from the ventilation. The peripheral muscular strength also increased markedly.

2.3.2. Biochemical data

Table 1 below gives a survey of the IGF-1 values (in ng/ml) and the urea content in blood (mg/dl) of the patient. A serum IGF-1 increase and a serum urea decrease are together considered signs of anabolism. A graphic representation of these results is shown in figure 2. This shows that the IGF-1 level rose during the treatment. In this specific patient the urea content in the blood was always low while a pronounced catabolism was nevertheless present. This can be explained by a substantial amount of nitrogen loss abdominally via the enterocutaneous fistulas.

Table 1

	IGF-1 values (ng/ml)	urea content (mg/dl)
day 0	108	51
day 3	258	58
day 8	296	48
day 15	373	50
day 22	251	54
day 29	442	46
day 37	n.d.	50
day 44	520	70
day 51	525	59

n.d. = not determined

EXAMPLE 3

3.1. Diagnosis

A female patient of 56 years of age was suffering from a sigmoid perforation on diverticulitis with faecal peritonitis and sepsis with multiple organ system failure. As a result she was being ventilated and subjected to continuous veno-venous haemofiltration as kidney replacement therapy. She displayed in addition low T3 syndrome. The low T3 syndrome is characterized by the following contents of thyroid hormones: TSH is 3.5 mIU/l; T4 is 2.9 µg/dl; T3 is 36 ng/dl. The patient was admitted to the intensive care unit after a secondary referral from a peripheral hospital because of her low T3 syndrome, drowsiness, pronounced cachexia and her dependance upon respiration equipment.

3.2 Therapy

26 days after admission to the intensive care unit without immediate improvement of the condition a treatment with growth hormone and T3 was started. On days 1 and 2 the

patient received 4 IU growth hormone, on days 3 to 5 inclusive a dose of 8 IU and on days 6 to 29 inclusive a dose of 16 IU, while 20 µg/day T3 was administered in a continuous infusion.

3.3 Evaluation

3.3.1. Clinical development

Under the therapy the wound healing improved progressively. The patient was fully ventilated up to and including day 4 of the growth hormone therapy. Thereafter however she could be withdrawn from the respiration equipment and was completely independent of mechanical support on day 27 of the treatment. On day 31 after starting of the treatment she was discharged from the intensive care unit. Her peripheral muscular strength had clearly increased, which was shown by kinesitherapeutic evaluation (results not given). Using an EEG a clear neurological as well as a psychological improvement was observed during this treatment.

3.3.2. Biochemical parameters

The IGF-1 and urea values were determined in blood by standard procedures. The results are given in table 2 below and are shown graphically in figure 3. The IGF-1 values increased while the urea level decreased, indicating anabolism.

Table 2

	IGF-1 values (ng/ml)	urea content (mg/dl)
day 0	64.5	104
day 3	93.8	75
day 6	157.3	70
day 11	208.2	64
day 15	227	63
day 22	n.d.	81
day 29	n.d.	51

EXAMPLE 4

4.1. Diagnosis

A female patient of 63 years of age who had an aorta valve replaced by an artificial valve twice underwent post-operative further surgery because of bleeding. In addition, she also displayed an idiopathic hypertrophic sub-valvular aorta stenosis. Her recovery progressed slowly, inter alia because of intercurrent pneumonia, critical illness polyneuropathy, pronounced pleural effusions and drowsiness. She had very low serum concentrations of the thyroid hormones (TSH is 0.3 mIU/l; T4 is 6.5 µg/dl; T3 is 23.1 ng/dl: and reverse T3 is 134 ng/dl), which indicates low T3 syndrome.

4.2 Therapy

The patient initially received T4 but because insufficient conversion to T3 occurred and the clinical result obtained was insufficient, a growth hormone treatment was likewise started. This took place 21 days after the operation for a total treatment duration of 8 days. On days 1 and 2 of the therapy she received 4 IU of growth hormone, on days 3-5 a dose of 8 IU and on days 6-8 a dose of 16 IU. On day 7 after the operation a start was made with T4 in a quantity of 50 µg/day gradually increasing to 150 µg/day.

4.3 Evaluation

4.3.1. Clinical development

The pleural effusions decreased slightly with administering of only T4. They only disappeared completely after combination therapy of T4 + growth hormone. Her peripheral muscular strength clearly increased, but only after the growth hormone therapy was started. In all other respects the patient experienced a surprisingly speedy recovery, which resulted in an early discharge from the intensive care unit. The growth hormone treatment was therefore also terminated prematurely.

4.3.2. Biochemical parameters

The IGF-1 and urea values were determined in blood by standard procedures. The results are given in table 3 below and are shown graphically in figure 4.

Table 3

	IGF-1 values (ng/ml)	urea content (mg/dl)
day -13 before starting T4	103	150
day -7 after 7 days T4	n.d.	82
day 1	55	56
day 3	60	54
day 8	71	33

An increase in the IGF-1 was observed after day 1 and a decrease in the urea level.

EXAMPLE 5

5.1 Diagnosis

A male patient of 23 years of age with an abdominal trauma with pancreatitis received a somatostatine infusion for treatment thereof. His thyroid hormone levels were as follows: TSH is 1 mIU/l; T4 is 2 µg/dl; T3 is 40 ng/dl and reverse T3 is 24 ng/dl. This indicates a pronouncedly low T3 syndrome. In addition the patient was in a catabolic condition and was dependant upon artificial respiration equipment.

5.2 Therapy

53 days after the trauma a 12 day course of treatment with growth hormone and T4 was started. On days 1 and 2 the patient received 4 IU growth hormone, on days 3-5 a dose of 8 IU and on days 6-12 a dose of 16 IU. From day 3 200 µg T4 was also administered.

5.3 Evaluation

5.3.1. Clinical development

The wound healing of the patient clearly improved under the growth hormone therapy. The ventilation had already been stopped by the time the growth hormone therapy started. The peripheral muscular strength very clearly increased, which was shown by means of a kinesitherapeutic evaluation (results not shown).

5.3.2. Biochemical parameters

Table 4 below shows a survey of the urea levels in the patient. The values are shown graphically in figure 4. The urea content clearly decreased, which signifies an improvement in the catabolic condition.

Table 4

	urea content (mg/dl)
day 1	187
day 3	171
day 6	94
day 10	52
day 12	49
day 14	51

EXAMPLE 6

6.1 Diagnosis

A male patient of 36 years of age had a cervical fracture luxation C6-C7 and a spinal cord lesion. The patient was dependent on ventilation on the one hand because of the paralysis and on the other hand because of muscular atrophy of the innervated respiratory muscles (bilateral diaphragm domes and the cervical auxiliary respiratory muscles). Additional problems were a cervical osteomyelitis, an oesophageal rupture and a tracheo-oesophageal fistula. After drainage of pus accumulations and applying oesophagotomy, followed by closure of the wound with a myocutaneous skin/muscle graft, healing did not however occur. The thyroid hormone values were as follows: TSH is 0.9 mIU/l; T4 is 3.6 μg/dl; T3 is 72 ng/dl; and reverse T3 is 64 ng/dl, indicating a low T3 syndrome.

6.2 Therapy

The growth hormone therapy was started to stimulate the immunity of the patient and increase the chance of recovery from these extremely infectious injuries. On days 1 and 2 4 IU of growth hormone was administered, on days 3-5 a dose of 8 IU and on days 6-34 a dose of 16 IU. In addition the patient continuously received 25 μg T3 a day intravenously.

6.3 Evaluation

6.3.1. Clinical development

The wound healing improved spectacularly after starting the endocrine treatment. Skin and muscle grafts grew in well, and all signs of infection disappeared over a period of about two weeks. Additional surgery was found to be unnecessary and this exceeded all expectations. The peripheral muscular strength of innervated muscles clearly increased, which was shown by means of kinesitherapeutic evaluation (not shown).

6.3.2. Biochemical parameters

Shown in table 5 below is a survey of the IGF-1 and urea levels in the patient.

	IGF-1 values (ng/ml)	urea content (mg/dl)
day 1	129	23
day 3	402	21
day 6	385	27
day 8	520	24
day 13	755	33
day 20	543	39
day 27	674	32
day 34	618	33

The values are shown graphically in figure 5. The IGF-1 values clearly increased while the urea content remained consistently low under an increased supply of proteins.

EXAMPLE 7

7.1 Diagnosis

A male patient of 48 years of age underwent a pneumonectomy for a lung abscess three weeks after lobectomy-superior for a lung neoplasm. Even before the operation the patient was suffering from catabolism. The operation the patient underwent was very aggressive. The right hemithorax was scraped, a pericardiectomy was performed and a thorax window was arranged in an infected environment. The chances for survival of the patient with the available conventional therapy were estimated to be virtually non-existent. The thyroid hormone contents were as follows: TSH is 0.1 mIU/l; T4 is 2 µg/dl; T3 is 28 ng/dl.

7.2 Therapy

The patient was treated with growth hormone and T3. Growth hormone was administered in a quantity of 4 IU on days 1 and 2, 8 IU on days 3-5, 16 IU on days 6-21, 8 IU on days 22-32 and 16 IU on days 33-84. T3 was administered by means of an infusion in a quantity of 25 µg/day.

7.3 Evaluation

7.3.1. Clinical development

Rinses of the right hemithorax were performed daily and a well granulating wound resulted progressively. On day 52 a revision was performed because of a small leak in the right bronchus stump, for which an omentumplasty was performed. Thereafter the wound healed perfectly and the right bronchus was definitively closed. Initially the patient was ventilated with a high frequency percussion respiration device (on days 1-7). It was possible thereafter to transfer to conventional ventilation (SIMV --- ASB). The pressure support could be reduced from day 37 but could not be withdrawn completely until after the revision of the bronchus leak was carried out on day 52. Hereafter it was possible to completely stop the artificial support of the respiration over a period of 21 days. From day 73 the patient breathed completely autonomously. This was described as unexpected and very exceptional by the vast majority of the attending physicians, since survival with one lung had been predicted as impossible on the basis of the pre-operative lung function test of the patient. The peripheral muscular strength clearly increased, which was demonstrated by means of kinesitherapeutic evaluation (results not given).

7.3.2. Biochemical parameters

Shown in table 6 below is a survey of the IGF-3, T3 and urea levels in the patient.

	IGF-1 values (ng/ml)	urea content (mg/dl)	T3 (ng/dl)
day 0	127	199	28
day 34	164	189	83
day 41	312	106	95
day 49	341	69	n.d.
day 54	398	92	105
day 61	258	98	91
day 68	413	80	129
day 75	579	78	150

The results are shown graphically in figure 6. IGF-1 increased, urea decreased and the T3 content became adequate under T3 treatment.

Using the present invention it is possible to withdraw from the support equipment quicker and more often than until now patients with a low T3 level, who have to be artificially ventilated or otherwise require supportive therapy. In addition the growth hormone therapy has a positive effect on a large number of other body functions, such as wound healing, muscular strength, neurological functions and psychological well-being.

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CLAIMS

1. Use of growth hormone to manufacture a pharmaceutical preparation for treating patients with a low triiodothyronine level.

2. Use as claimed in claim 1, **characterized in that** the low triiodothyronine level is the result of the low T3 syndrome.

3. Use as claimed in claim 1 or 2, **characterized in that** the growth hormone is recombinant growth hormone.

4. Use as claimed in claim 1, 2 or 3, **characterized in that** the growth hormone is recombinant human growth hormone.

5. Use as claimed in any of the claims 1-4, **characterized in that** the low triiodothyronine level or low T3 syndrome in the patient is caused by one or more clinical conditions selected from the group consisting of premature birth, old age, fasting, undernourishment, anorexia nervosa, depression, anxiety syndromes, stress disorders, liver disfunction, kidney disfunction, systemic illness, chronic heart decompensation, COLD, sepsis, trauma, post-operative condition, critical illness, increase in the endogenous dopamine level.

6. Use as claimed in any of the claims 1-4, **characterized in that** the low triiodothyronine level or low T3 syndrome in the patient is caused by use of medicine or dopaminergic medication.

7. Use as claimed in claim 6, **characterized in that** the medicine used is selected from the group consisting of propylthiouracyl, glucocorticoids, amiodaron, d-propanolol, oral cholecystographic agents, somatostatine, dopaminergic medicines.

8. Use as claimed in claim 6, **characterized in that** the dopaminergic medicines are selected from the group consisting of dopamine, dopamine-agonists such as bromocryptine, cabergoline, epinine, dopamine precursors and precursors of dopamine-agonists such as ibopamine.

9. Pharmaceutical composition comprising growth hormone, peptides or other molecules which stimulate growth hormone secretion, and one or more compounds selected from the group of thyroid hormones and anabolic steroids together with a pharmacologically acceptable diluent.

10. Pharmaceutical composition as claimed in claim 9, **characterized in that** the thyroid hormones comprise thyroxine (T4) and triiodothyronine (T3).

11. Pharmaceutical composition as claimed in claim 9, **characterized in that** the anabolic steroids are selected from the group consisting of androgens, oestrogens, their natural or synthetic analogues and combinations thereof.

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INTERNATIONAL SEARCH REPORT

Inter ..al Application No
PCT/BE 95/00022

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/27 //(A61K38/27,31:195)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO-A-93 04694 (NOVO NORDISK) 18 March 1993 see the whole document	1,5
X	WO-A-91 11196 (NOVO NORDISK) 8 August 1991 see the whole document	1,5
X	WO,A,90 09189 (BRIGHAM AND WOMEN'S HOSPITAL) 23 August 1990 see the whole document	1,5
P,X	WO,A,95 00167 (PHARMACIA AB) 5 January 1995 see the whole document	1,5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 June 1995	21 -06- 1995

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Moreau, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/BE 95/ 00022

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
See annex.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

The search concerning the pharmaceutical compositions has been limited to the compositions containing growth hormone excluding its replacement by other peptides or molecules stimulating the release of growth hormone (see claim 9), this aspect being not supported by the description, and no examples of such other peptides or molecules are given.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr al Application No
PCT/BE 95/00022

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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